



FINAL CLINICAL STUDY REPORT

Study Title: A Multicenter Phase II, Open-Label Study to Evaluate the Pharmacokinetics of Tacrolimus or Cyclosporine when Coadministered with Adefovir Dipivoxil 10 mg to Patients Post-Liver Transplantation

Name of Test Drug: Adefovir Dipivoxil

Indication: Chronic Hepatitis B

Sponsor: Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Study No.: GS-02-531

Phase of Development: Phase 2

IND No.: 52,182
EudraCT No.: Not Applicable

Study Start Date: 18 February 2004 (First Subject Screened)
Study End Date: 31 May 2005 (Last Subject Observation for Follow-up)

Principal or Coordinating Investigator: Name: Norah Terrault, MD
Affiliation: University of California, San Francisco
San Francisco, CA

Gilead Responsible Medical Monitor: Name: Jeffrey Enejosa, MD

Report Date: 27 October 2005

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was performed in compliance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Multicenter Phase II, Open-Label Study to Evaluate the Pharmacokinetics of Tacrolimus or Cyclosporine when Coadministered with Adefovir Dipivoxil 10 mg to Patients Post-Liver Transplantation
Investigators: Multicenter study; principal investigator was Norah Terrault, MD; Appendix 4 contains a complete list of investigators
Study Centers: The study was initiated at 12 centers in the United States; five of those centers enrolled subjects.
Publications: None
Study Period: 18 February 2004 (First subject screened) 31 May 2005 (Last subject observation for follow-up)
Phase of Development: Phase 2
Objectives: The primary objective of this study was as follows: <ul style="list-style-type: none">• To evaluate pharmacokinetics of tacrolimus or cyclosporine when administered alone and coadministered with adefovir dipivoxil 10 mg once daily in patients post-liver transplantation The secondary objectives were as follows: <ul style="list-style-type: none">• To evaluate the pharmacokinetics of adefovir dipivoxil 10 mg once daily when coadministered with tacrolimus or cyclosporine in patients post-liver transplantation• To evaluate the safety of adefovir dipivoxil 10 mg once daily when coadministered with tacrolimus or cyclosporine

STUDY SYNOPSIS (CONTINUED)

Methodology: This was a multicenter, Phase-2, open-label, sequential-cohort, drug-interaction study. Cohort-1 subjects (tacrolimus + adefovir dipivoxil) were enrolled first. Based on the findings in Cohort 1, a decision was made on whether to enroll subjects in Cohort 2 (cyclosporine + adefovir dipivoxil) (i.e., if no interaction was observed in Cohort 1, Cohort-2 subjects would not be enrolled). Since no pharmacokinetic interaction was observed in Cohort 1, Cohort 2 was not enrolled.

Number of Subjects (Planned and Analyzed):

Planned: Up to 44 subjects (up to 22 per cohort)

Enrolled: 16 subjects (Cohort 1 only)

Analyzed: Pharmacokinetics: 16 subjects

Safety: 16 subjects

Because of slow enrollment, data from 16 completed Cohort-1 subjects were evaluated. This analysis indicated that the study had adequate statistical power to meet the study objectives.

Diagnosis and Main Criteria for Inclusion: Male and nonpregnant female subjects 18 through 65 years of age who had undergone liver transplantation ≥ 6 months before enrolling in the study; who had calculated creatinine clearance ≥ 50 mL/min with $\leq 20\%$ change over a 3-month period; and who were on a documented stable dose of tacrolimus (Cohort 1) or cyclosporine (Cohort 2) for 3 months before enrollment

Duration of Treatment: Each cohort was to receive adefovir dipivoxil treatment for 14 days. Tacrolimus treatment (Cohort 1) was ongoing at enrollment and continued throughout.

Test Product, Dose, Mode of Administration, and Batch No.: Adefovir dipivoxil: One 10-mg tablet per day, taken orally on study Days 1 through 14; Lots No. TDJ015 and D301B2

Reference Therapy, Dose, Mode of Administration, and Batch No.: Tacrolimus: Subjects continued taking their regular prescribed dosage regimen, as obtained from their regular pharmacy.

STUDY SYNOPSIS (CONTINUED)

Criteria for Evaluation:

Pharmacokinetics: Pharmacokinetic assessments were performed on blood and urine samples collected at baseline (Day 0) during treatment with tacrolimus alone, and on Days 2, 7, and 14 during coadministration of adefovir dipivoxil and tacrolimus. On Days 0 and 14, serial blood samples were obtained over a 12- to 24-hour period, and urine was collected over specified intervals throughout the same time period.

The following pharmacokinetic parameters were determined for adefovir dipivoxil and tacrolimus: C_{max} , T_{max} , C_{last} , T_{last} , AUC_{tau} , AUC_{0-last} , k_{el} , $T_{1/2}$, Vz/F , CL/F , and $C_{trough/min}$.

After all subjects in Cohort 1 (tacrolimus) completed the study, a pharmacokinetic analysis was to be conducted to determine if a drug-drug interaction was detectable. If no interaction was observed, Cohort-2 (cyclosporine) subjects would not be enrolled.

Safety: Safety was evaluated by documentation of adverse events (AEs), by assessment of clinical laboratory findings, and by physical examination, including measurement of vital signs and weight.

Statistical Methods:

Pharmacokinetics: Pharmacokinetic parameters were calculated using noncompartmental methods using a pharmacokinetic data analysis program (WinNonlin). The area under the curve was calculated using the linear/log trapezoidal rule. Ninety percent (90%) confidence intervals were constructed around the ratio of geometric means of AUC and C_{max} for tacrolimus when dosed alone and when coadministered with adefovir dipivoxil. If the 90% confidence interval about the ratio of geometric means was within the equivalence bounds of 80% to 125%, it would be concluded that there was no alteration in the pharmacokinetics of tacrolimus. It would be concluded that there was no alteration in the pharmacokinetics of adefovir if the data from this study were comparable to historical data from Gilead pharmacokinetics Studies GS-00-472 and GS-00-476 in which adefovir dipivoxil was administered alone.

If no evidence of a drug-drug interaction was seen after analysis of pharmacokinetic parameters for the tacrolimus cohort (Cohort 1), the inclusion of the cyclosporine cohort (Cohort 2) would be deemed unnecessary.

Safety: The incidences of AEs and laboratory abnormalities were summarized using subject count and percentages. Changes from baseline in hematology and clinical chemistry parameters and in weight and vital signs parameters were summarized using descriptive statistics, including sample size, mean, median, standard deviation, interquartile range (Q1, Q3), and minimum and maximum values.

STUDY SYNOPSIS (CONTINUED)

SUMMARY – RESULTS:

Pharmacokinetic Results: The dose-normalized (1 mg) mean (%CV) primary pharmacokinetic parameters for tacrolimus administered alone (Day 0) and together with adefovir dipivoxil (Day 14), and the results of the statistical analysis are summarized below:

Dose-Normalized Tacrolimus Pharmacokinetic Parameter	Geometric Least Squares Means		Geometric Least Squares Mean Ratio	90% Confidence Interval
	Day 14 (Tacrolimus with Adefovir Dipivoxil) (N = 16)	Day 0 (Tacrolimus Alone) (N = 16)		
C _{max} (ng/mL)	7.38	7.02	1.052	0.898–1.232
AUC _{tau} (ng•h/mL)	48.88	45.93	1.064	0.929–1.219

The limits of the 90% confidence intervals for the geometric mean ratios (Day 14/Day 0) were contained within the specified bounds of 80% to 125% for the dose-normalized primary pharmacokinetic parameters of tacrolimus (see above table). Thus, the coadministration of adefovir dipivoxil did not alter the pharmacokinetics of tacrolimus.

In addition, the pharmacokinetic properties of adefovir following coadministration with tacrolimus were similar to those observed in previous pharmacokinetic studies of adefovir dipivoxil administered alone. Thus, the coadministration of tacrolimus did not appear to alter the pharmacokinetics of adefovir.

Safety Results: Ten subjects (62.5%) had a total of 25 treatment-emergent AEs. These AEs were consistent with the known safety profiles of the drugs in this patient population. There were no serious AEs, and no subject discontinued due to an AE. Only one AE occurred in more than a single subject: cough, which was reported for two subjects (12.5%). There were two severe AEs, both judged by the investigator to be unrelated to treatment and neither leading to discontinuation of study treatment: elevated alanine aminotransferase (ALT) on Day 21 in a subject who also had elevated ALT prestudy and at each subsequent assessment; and in another subject, elevated creatine phosphokinase (CPK) on Day 14 that returned to normal by Day 21. One AE was judged by the investigator to be possibly/probably related to study treatment: mild abdominal distention that resolved with simethicone treatment. Five subjects had a total of seven Grade-3 or 4 laboratory abnormalities during study treatment, each judged by the investigator not to be clinically significant. The most common Grade-3 or 4 laboratory abnormality was 3+ blood in urine (Grade 3), which occurred in three female subjects and was associated with menses in each subject.

STUDY SYNOPSIS (CONTINUED)

CONCLUSIONS: Coadministration of adefovir dipivoxil did not alter the pharmacokinetics of tacrolimus, and the pharmacokinetic parameters of adefovir in this study were comparable to those observed in previous studies (GS-00-472 and GS-00-476). In addition, coadministration of adefovir dipivoxil and tacrolimus was found to be safe. There were no serious AEs or discontinuations for AEs, and the reported AEs were consistent with the known safety profiles of the drugs in this patient population.